

REMARKS

Amendments

Claim 1 has been amended to specify a vaccine composition rather than a pharmaceutical composition. Claim 1 has also been amended to specify that the antigen is not structurally changed by "chemical protein conjugation." Support for this amendment can be found in, for example, paragraph 21 of the published application.

Claim 3 has been amended to make it grammatically correct.

Claims 21-26 directed to a non-elected invention have been canceled without prejudice to filing in a divisional application.

Claims 27 and 28 have been amended to be consistent with the remaining claims.

Applicants submit that the above amendments do not add any new matter, and their entry is requested.

Oath

Applicants note that a substitute Declaration is required and are in the process of obtaining the necessary signatures for this declaration. However, because several inventors are located in other countries, obtaining the necessary signatures is requiring more time. A substitute Declaration will be submitted as soon as it is fully executed.

Summary of the Present Invention

The present invention is directed to a vaccine composition that potentiates the immunogenicity of low immunogenic antigens. The composition comprises the low immunogenic antigens and a vaccine carrier. The vaccine carrier consists of very small size proteoliposomes (VSSPs). The VSSPs are derived from the Outer Membrane Protein Complex (OMPC) of *Neisseria meningitidis* and include gangliosides that have been incorporated into the OMPC. The low immunogenic antigens are selected from the group consisting of peptides, polypeptides, proteins and their corresponding nucleic acid sequences. The antigens have not been structurally modified, i.e.,

they remain in the native form, and have not been incorporated into the VSSPs. As described in the specification, the antigen has not been modified by chemical protein conjugation. The vaccine carrier stimulates and potentiates the immune response against the low immunogenic antigen. Both the humoral immune response and the cellular immune response are stimulated and potentiated by the vaccine carrier. As noted, the immune response is against the low immunogenic antigen which is a peptide, etc. as set forth in the claims. The potentiation of the cellular immune response includes a potentiation of the induction ability of cytotoxic T cells, such as CD8⁺ T cells as shown in Example 18.

Rejection Under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 1, 3-11 and 27-29 under 35 U.S.C. § 112, second paragraph for being indefinite with respect to the phrase “wherein the antigen is not structurally changed.” The Examiner contends that this phrase is not clear because the peptides exemplified in the application, e.g., an extracellular domain of HER-1, has been structurally changed with respect to the native protein.

Applicants do not believe that the Examiner is correct in this rejection. Applicants note that the Examiner does not appear to be considering the term “antigen” as used in the present specification and as used in the art, which is the material that is administered to produce an immune response. As noted by the Examiner, the antigen may be a structurally modified peptide, e.g., an extracellular domain of HER-1. Although the antigen may be a structurally modified peptide when compared to the native protein, the antigen as delivered in the composition, i.e., the extracellular domain of HER-1, is not structurally modified. That is, the structurally modified peptide is the antigen, and the antigen is not structurally modified.

Although Applicants believe that the phrase objected to by the Examiner is definite to the skilled artisan, they have nevertheless amended claim 1 to clarify that the antigen has not been structurally changed by chemical protein conjugation. Applicants submit that the claimed subject matter is definite to the skilled artisan.

For all of the above reasons, Applicants submit that the claims are definite. Withdrawal of this rejection is requested.

Rejection Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1, 3-11 and 27-29 under 35 U.S.C. § 103(a) as being obvious over Rodriguez et al. (US 5,788,985) in view of Estevez et al. (*Vaccine* **18**:190-197, 2000), Hammonds (US 4,857,637) and Udayachander et al. (*Human Antibodies* **8**:60-64, 1997). Applicants traverse this rejection.

The Examiner cites Rodriguez et al. '985 for its disclosure of a pharmaceutical composition comprising the OMPC of *Neisseria meningitidis* into which gangliosides, especially N-glycolyl GM3, has been incorporated (i.e., VSSPs). The Examiner further cites Rodriguez et al. '985 for its disclosure that the pharmaceutical composition increases the immune response against N-glycolylated ganglioside which can be used for treating cancer, especially breast cancer which has a higher expression of gangliosides GM3 and GD3. The Examiner concludes that Rodriguez et al. teach that gangliosides are targets in treatment approaches. The Examiner notes that Rodriguez et al. does not teach that the pharmaceutical composition further comprises a low immunogenic antigen (such as HER-1) or an adjuvant (such as Incomplete Freund's adjuvant) and that Rodriguez et al. does not teach that the pharmaceutical composition stimulates both humoral and cellular responses against the low immunogenic antigen.

The Examiner contends that Estevez et al. discloses that the VSSPs stimulates cellular and humoral immune responses. Specifically, the Examiner contends that Estevez et al. discloses that immunization using OMPC with incorporated gangliosides results in significant levels of T-dependent IgG1, IgG2a and IgG2b demonstrating a cellular immune response, as well as significant levels of T-independent IgG3 and IgM demonstrating a humoral response immune response. The Examiner cites the abstract for the disclosure that VSSPs overcame the natural tolerance to low-immunogenic self-antigen gangliosides in an adjuvant-dependent fashion. The Examiner cites page 196 for the disclosure that it was known that the serotype proteins that are the main components of

the OMPC induce proliferation and activation of lymphocytes and lead to the secretion of IL-2. The Examiner also notes that Estevez et al. teach the immunization using Incomplete Freund's adjuvant Montanide ISA 51 with the VSSPs, and that Montanide ISA 51 is preferred because it is less toxic than Incomplete Freund's Adjuvant. The Examiner also states that Estevez et al. discloses that mice immunized with VSSPs derived from the OMPC of *Neisseria meningitides* with gangliosides incorporated therein in combination with Montanide ISA 51 resulted in increased immunoglobulin titres compared to mice immunized with VSSPs without Montanide ISA 51. The Examiner further cites Estevez et al. for teaching that patients suffering from metastatic breast cancer have been immunized with GM3/VSSP and NGcGM3/VSSP vaccines in Montanide ISA 51 for therapy.

The Examiner cites Hammonds et al. for its disclosure of a pharmaceutical composition comprising EGFR (i.e., HER-1) as an antigen to immunize animals against EGFR and for its disclosure that EGFR is overexpressed in malignant cells and thus is a desirable target for therapy. The Examiner also notes that Hammonds et al. teaches that immunization may comprise administering growth factor receptor derivatives or intact receptors, which would not be structurally changed. The Examiner further contends that Hammonds et al. also discloses the use of an adjuvant, such as Incomplete Freund's Adjuvant, for immunization with growth factor receptors.

The Examiner cites Udayachander et al. for its disclosure that many malignancies, such as breast cancer, overexpress EGFR and that EGFR is a target for therapy.

The Examiner then contends that each of these references suggest the importance of each of the claimed pharmaceutical components in stimulating an immune response to the ganglioside or EGFR antigen. The Examiner then notes that the references are deficient in that they do not teach using these components together. However, the Examiner concludes that it would be *prima facie* obvious to use the OMPC of *Neisseria meningitides* into which ganglioside antigens have been incorporated as taught by Rodriguez et al. '985 and Estevez et al. and the EGFR antigen of Hammonds et al. in order to treat malignant tumors that overexpress these two antigens, such as breast cancer, because Rodriguez et al. '985 and Udayachander et al. teach that breast cancer overexpresses these antigens. The Examiner contends that it would have been obvious to combine

two modes of treatment since the idea of combining them flows logically from each mode having been taught in the prior art. The Examiner contends that a skilled artisan would have reasonably expected to obtain effective therapeutic targeting of malignant tumors because both antigens were shown to elicit an immune response. The Examiner also contends that it would have been obvious to use an adjuvant in conjunction with the two antigens in view of the teachings of Hammonds et al. and Estevez et al. Although the Examiner notes that the references do not teach the stimulation of both humoral and cellular immune response, the Examiner contends that the composition taught by the prior art would necessarily induce both immune responses since the composition of the combined references comprises the same components as the claimed subject matter. Thus, the Examiner contends that the composition taught by the prior art would necessarily induce both a humoral and cellular immune response against a low immunogenic antigen such as HER-1.

In discussing Applicants' prior arguments concerning patentability, most of the Examiner's comments relate to the previous arguments concerning surprisingly found adjuvant property of VSSPs. The Examiner cites and discusses four references (pages 11-12) which the Examiner claims teaches that proteosomes prepared from OMPC were known to act as both a carrier and an adjuvant and that the proteosomes themselves have adjuvant properties. The Examiner argues it is clear from this art that the proteosome confers enhanced immune responses to the peptide it is administered with because of its adjuvant properties, whether the peptide is coupled to the proteosome or not. Thus, the Examiner concludes that adjuvant properties of proteosomes for inducing humoral and cellular immune responses to low immunogenic peptides in the prior art are known and reasonably expected for the composition taught by the prior art. Applicants submit that the cited references do not support the Examiner's position, and in fact, teach away from the presently claimed invention because they teach that chemical protein conjugation is required.

Specifically, Applicants note that all of the cited references (Lowell, US 5,726,292; Lowell et al., *Science* **240**:800-802, 1988; Levi et al., *Vaccine* **13**:1353-1359, 1995; and VanCott et al., *J Immunology* **160**:2000-2012, 1998) clearly teach using antigens that are chemically conjugated with another molecule so that they are incorporated into the proteosome. For example, Lowell '292

discloses chemically conjugating a hydrophobic foot or hydrophobic anchor to the small peptide which is then complexed with the proteosome. See, column 4, lines 39-42 and 59-61; column 6, lines 21-26; and column 8, lines 34-48. Similarly, Lowell et al. (1995) discloses chemically conjugating a hydrophobic anchor to a small peptide that contained tandem repeats of malaria CS proteins. See, Table 1, page 800. This chemically conjugated antigen was complexed with the proteosome. See, page 800, middle column, first full paragraph. Levi et al. (1995) also describe chemically conjugating a hydrophobic anchor to the small peptide antigen and complexing this structurally modified antigen to a proteosome. See, page 1354, column 1 under "Synthetic Peptides" and page 1355, right column, first sentence under "Results." Finally, VanCott et al. (1998) states that the proteosomes were prepared as described by two references, one of which is Lowell et al. (1995) and the other of which is a further Lowell et al. paper. See, page 2001, right column under "Immunogen and adjuvants." According to Lowell et al. (1995), as noted above, the antigen is conjugated with a hydrophobic anchor which is then complexed with the proteosome. In addition, Applicants note that Lowell is an author on all of these references. This fact further evidence that all of the proteosomes including an antigen would have included a peptide antigen chemically conjugated to a hydrophobic anchor which is then complexed with proteosomes. Thus, Applicants submit that these references clearly teach to the skilled artisan that it was necessary to chemically conjugate a hydrophobic anchor to a low immunogenic peptide and then complex the chemically conjugated peptide with proteosomes in order to generate an immune response. There is nothing in this art that suggests that the immunogenicity of a low immunogenic peptide could be potentiated without chemically conjugating the low immunogenic peptide to a hydrophobic anchor and without complexing the conjugated peptide with proteosomes. In view of these teachings in the prior art, Applicants submit that the prior art teaches away from the claimed invention.

Applicants also note that Estevez et al., which is directed to a low immunogenic ganglioside and not a low immunogenic peptide, discloses that the ganglioside must be complexed with proteosomes in order to potentiate the immunogenicity of the ganglioside. Since the ganglioside contains a hydrophobic portion, it is able to complex with the proteosomes without chemical

conjugation. As shown by the references cited by the Examiner, the prior art taught that the low immunogenic peptides were chemically conjugated with a hydrophobic anchor prior to incorporation into the proteosomes. The prior art does not teach or suggest that the immunogenicity of low immunogenic peptides could be potentiated by a vaccine composition that contains a low immunogenic peptide that is not structurally changed by chemical protein conjugation and is not incorporated, i.e., complexed, with the proteosomes. In fact, the prior art teaches exactly the opposite, i.e., that it is required to structurally alter the low immunogenic peptide by chemically conjugating a hydrophobic anchor and that this structurally altered peptide is incorporated into the proteosomes.

The claimed subject matter is a vaccine composition that comprises VSSPs and a low immunogenic antigen (i.e., peptides, polypeptides, proteins and corresponding nucleic acids) which is not structurally changed and which is not incorporated into the VSSPs. Such a composition is not shown or suggested by the cited prior art, and as detailed above, is specifically taught away from by the prior art references cited by the Examiner on pages 11-12 of the Office Action. Thus, Applicants submit that the combined teachings of Rodriguez et al., Estevez et al., Hammonds and Udayachander et al. do not render the presently claimed subject matter obvious.

In view of the above amendments and remarks, it is submitted that the claimed subject matter is not obvious from the teachings of Rodriguez et al., Estevez et al., Hammonds and Udayachander et al. Withdrawal of this rejection is requested.

Concluding Remarks

In view of the above amendments and remarks, it is believed that the present claims satisfy the provisions of the patent statutes and are patentable over the cited prior art. Reconsideration of

Application Serial No. 10/003,463
Amendment Dated 18 August 2009
Reply to Office Action dated 23 February 2009

the application and early notice of allowance are requested. The Examiner is invited to telephone the undersigned to expedite the prosecution of the application.

Respectfully submitted,
ROTHWELL, FIGG, ERNST & MANBECK, p.c.

By /Jeffrey L. Ihnen/
Jeffrey L. Ihnen
Registration No. 28,957
Attorney for Applicants
1425 K Street, N.W., Suite 800
Washington, D.C. 20005
Telephone No.: (202) 783-6040
Facsimile No.: (202) 783-6031

1640725_1